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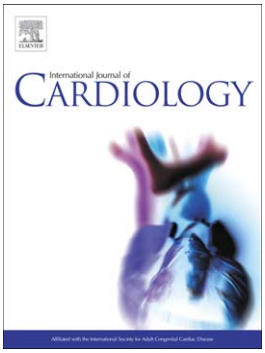

Asymptomatic Versus Symptomatic Atrial Fibrillation: A Systematic Review of Age/Gender Differences and Cardiovascular Outcomes

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ASYMPTOMATIC VERSUS SYMPTOMATIC ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW OF AGE/GENDER DIFFERENCES AND CARDIOVASCULAR OUTCOMES

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ABSTRACT

Up to 40% of atrial fibrillation (AF) patients are asymptomatic. Despite this, scarce data are available about asymptomatic AF, with regard to its clinical profile and relationship to cerebrovascular and cardiovascular risk. Our objective was to conduct a systematic review and meta-analysis was to study the relationship between age and gender with asymptomatic AF and to establish whether patients with asymptomatic AF have a higher risk of death (all cause and cardiovascular) and stroke/systemic thromboembolism, when compared to symptomatic AF patients.

After a comprehensive search, 6 studies (2 randomized clinical trials and 4 observational studies) were entered in the meta-analysis.

Despite significant heterogeneity, our data show that the prevalence of females amongst asymptomatic AF group was significantly less compared to the symptomatic AF group (RR, 0.57; 95%CI: 0.52-0.64). No difference in age between asymptomatic and symptomatic AF patients (P=0.72) was seen.

No differences were found in all-cause death between patients with asymptomatic and symptomatic AF (RR, 1.38; 95%CI: 0.82-2.17), nor in cardiovascular death (RR, 0.85; 95%CI: 0.53-1.36) or stroke/thromboembolism (RR, 1.72 95%CI: 0.59-5.08).

Asymptomatic AF is more associated with male sex, irrespective of age. Both general and cardiovascular death risks as well as thromboembolic risk do not seem to be affected by the asymptomatic clinical status. Symptomatic status should not determine our approach to stroke prevention and other cardiovascular prevention therapies, amongst patients with AF.

KEY WORDS: asymptomatic, symptomatic, atrial fibrillation, cardiovascular death, stroke.

INTRODUCTION

Atrial fibrillation (AF) represents one of the most diagnosed supraventricular arrhythmia and its prevalence has been estimated to be 1-2% of the general population, with a progressive increase over the next few decades(1). However, prevalence data of AF could have been underestimated due to the evidence that up to 40% of AF patients are asymptomatic(2). Despite this, scarce data are available about asymptomatic AF, with regard to its clinical profile and relationship to cerebrovascular and cardiovascular risk.

Recent data from the EORP-AF Pilot Registry confirmed a high prevalence of asymptomatic AF patients, almost 40%(3). Importantly, the EORP-AF data show that asymptomatic AF patients were at a higher risk for 1-year mortality compared to symptomatic AF patients(3). Conversely a substudy from the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial suggested that there is no difference in mortality risk between asymptomatic and symptomatic AF patients(4). Furthermore, trial data from the Cryptogenic Stroke and Underlying AF (CRISTAL AF) study show how could be possible to detect AF, regardless of symptoms, in about 4% in a cohort of patients diagnosed with cryptogenic stroke(5).

An understanding of the clinical profile of asymptomatic AF patients and the impact on a higher thromboembolic risk could help plan established AF screening programs that could lead to earlier AF diagnosis and a reduction in the AF-related health burden(6).

The aim of this systematic review and meta-analysis of available evidence was to study the relationship between age and gender with asymptomatic AF and to establish whether patients

with asymptomatic AF have a higher risk of death (all cause and cardiovascular) and stroke/systemic thromboembolism, when compared to symptomatic AF patients.

METHODS

Inclusion and Exclusion Criteria

We included eligible studies published in English that focused on the comparison between asymptomatic AF and symptomatic AF, in line with the following criteria:

i. *Types of studies:* randomized controlled trials or observational cohort studies;
ii. *Types of participants*: AF patients divided into symptomatic and asymptomatic groups;
iii. *Types of outcome measures*: endpoints of all mortality, cardiovascular death, stroke, or thromboembolism event; and
iv. *Other variables of interest*: available baseline characteristics of AF patients according to the presence of symptoms

Duplicate studies were excluded, as were certain publication types, such as conference abstracts, comments, editorials, case reports, etc.

Search Strategy

An extensive search for available studies was performed in three major medical literature databases: PubMed, Scopus and the Cochrane Database. Terms used for the search were as follows: (asymptomatic OR symptomatic) AND atrial fibrillation. The electronic search was restricted to peer-reviewed journals. Clinical trial databases and relevant reviews were hand searched for potentially relevant studies not identified in the electronic database search.

Data Extraction and Management

All data retrieved from the PubMed, Scopus and Cochrane Database were managed using the commercial reference management software (Endnote X7, Thomson Reuters). Data extraction was performed by two reviewers (QX and MP) independently. The first sift-prescreening was completed through reading titles and then reading abstract and comprehensively reviewing full text to get hold of extra information did the second sift-selection. Data extracted from each study were, when available: mean age, gender distribution, follow-up time, overall all-cause death, cardiovascular death, stroke and/or systemic thromboembolism. Disagreements were resolved by consensus or, if necessary, through discussion or consultation with a third reviewer (GL).

The outcomes of interest included all-cause death, cardiovascular death, ischemic stroke/thromboembolism, quality of life, cardiovascular hospitalization, and AF progression.

Quality and Risk of Bias Assessment

A quality assessment process was performed to select the studies included in the meta-analysis. The pre-specified criteria for the evaluation were: (i) the total number of patients enrolled in the study would have been more than 300; (ii) at least one year of expected follow-up; (iii) data available for crude outcomes taken separately. To be included in the meta-analysis each study had to meet all the criteria. According to the design-specific recommended criteria, every study was evaluated for any potential risk of bias(7).

Statistical Analysis

Statistical analyses were performed using Review Manager Version 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The endpoint events were

measured as dichotomous outcome variables and compared between asymptomatic AF and symptomatic AF groups. Gender was also defined as dichotomous variable to investigate the gender distribution difference between both groups. Relative risk (RR) or odds ratio (OR) were analyzed and presented with 95% confidence interval (CI) for the pooled differences. Data required for dichotomous variables were the numbers of events and total numbers for each study, while means and its standard deviations were analyzed for continuous variables. Cochrane's chi-square test and were detected to quantify the statistical heterogeneity among included studies. Chi-square test evaluates whether the observed inconsistency may be due to chance alone. The I^2 statistic describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error. A rough guide to interpretation of the I^2 is as follows: 1) 0% to 25%: might not be important; 2) 25% to 50%: may present moderate heterogeneity; 3) 50% to 75%: may present substantial heterogeneity; 4) 75% to 100%: considerable heterogeneity.

The appropriate statistical models, fixed-effect or random-effect models, were selected to ensure that the various statistics are estimated correctly. Subgroup analyses were performed when necessary. A P value<0.05 was considered significant difference.

RESULTS

Based on our search, we identified 530 articles on the Cochrane Database, 3,347 on PubMed and 4,163 on Scopus. After checking for duplicates we reviewed a total of 4,163 articles. Two investigators reviewed all titles, obtaining a list of 35 articles to be reviewed by abstract and full text. Following this, 6 articles were found to be eligible for analysis (Figure 1).

Study Characteristics

Among these six studies, two trials were substudies from randomized controlled trials (RCTs), that is, the AFFIRM study(4) and the RAte Control versus Electrical cardioversion for persistent atrial fibrillation (RACE) study(8). The remainder were observational cohort studies(3, 9–11).

The baseline characteristics of all included studies are summarized in Table 1. A total of 2,534 patients (717 female; 28.3%) with asymptomatic AF and 7,774 patients (3,082 female; 39.6%) with symptomatic AF were included. The mean length of follow-up ranged from 1 to 9.9 years.

In the study from Boriani et al. the only asymptomatic portion was 16.7% of the total study population, as identified (3). Characteristics on thromboembolic risk stratification and antithrombotic treatment between the two populations in the various studies are summarized in Table 2. Due to the heterogeneity between the different study designs, these characteristics were not meta-analyzed.

Risk of bias assessment

Every study was evaluated for any potential risk of bias(7). All the articles included in the meta-analysis had an overall *low risk* of bias, as reported in Table 3. Risk of bias for every domain was defined as high, low or unclear. Overall bias risk for each study was determined with a risk level of at least 4 out of 5 domains.

Data synthesis

(a) Gender differences

In the present meta-analysis, female gender was defined as a dichotomous variable to be compared between asymptomatic and symptomatic AF groups. Considerable heterogeneity was measured when we performed pooled analyses of all six included studies, as reflected by I^2 as high as 70%. Given that the different type of studies can potentially be associated with the variability between studies, subgroup analyses were carried out accordingly. In addition, a random effects model was used for meta-analysis due to the high heterogeneity.

The comparison of gender differences between two groups is shown as a forest plot in Figure 2. The I^2 statistics were 52% and 37% in each subgroup analysis, representing moderate heterogeneity, which can be acceptable. The prevalence of females amongst asymptomatic AF patients was significantly less compared to the symptomatic AF group (RR, 0.57; 95%CI: 0.52-0.64).

(b) Age differences

When comparing the age difference between asymptomatic and symptomatic AF patients, five of all included studies were included for pooled analysis, except for the EURO-AF pilot general registry that only reported the median of age for both groups. When data were pooled across the remaining five studies, including mean age and SD, moderate heterogeneity was evident

significant, with no difference in age between asymptomatic and symptomatic AF patients (P=0.72) (Figure 3).

(c) All cause death

All-cause mortality was available in four of these included studies. The heterogeneity of these studies was considerable, as reflected by I^2 statistic as high as 75%, and this, a random effect model was adopted for pooled analysis. No difference was found in all-cause death between patients with asymptomatic and symptomatic AF (RR, 1.38; 95%CI: 0.82-2.17) as shown in Figure 4. Given the high heterogeneity, the interpretation of this result should be more cautious.

(d) Cardiovascular death

Among all included studies, four reported the outcome of CV death. When these data were extracted for pooled analysis, no significant difference between asymptomatic and symptomatic AF patients (RR, 0.85; 95%CI: 0.53-1.36) was seen, as shown in Figure 5. The I^2 statistic of 0% represented very low heterogeneity, indicating that these studies are regarded homogeneous.

(e) Stroke/thromboembolism

All included studies were divided into two subgroups (RCT, observational studies) for the pooled analysis due to the high heterogeneity. No difference of stroke/TE occurrence was found in the RCT subgroup, along with an I^2 statistic of 0%. In the analysis of observational studies, two individual studies has shown that the risk of stroke/TE was higher in patients with asymptomatic AF (RR, 8.89; 95%CI: 3.38-23.37 and RR, 2.19; 95%CI: 1.17-4.11, respectively). However, the overall pooled estimate demonstrated no significant difference in

stroke/TE between both groups (RR, 1.72 95%CI: 0.59-5.08) as shown in Figure 6. The high heterogeneity should be taken into account when interpreting this result.

DISCUSSION

In this systematic review and meta-analysis, our data suggest that male sex is significantly associated with asymptomatic AF, whilst no difference was seen in age. Second, asymptomatic AF was similar to symptomatic AF in the risk of overall risks of death, CV death or stroke/thromboembolic events.

Gender-related differences in the epidemiology, clinical characteristics and management of AF patients are well described(12–14). There is usually a higher incidence of AF in men than in women(15). However, women with AF are at higher risk of stroke and thromboembolism, particularly elderly women(16). Treatment of AF also varies among men and women, with regard to antithrombotic therapy and the choice of rate or rhythm control(12).

In the present meta-analysis, a lower prevalence of asymptomatic AF was observed in women than in men, as reflected by RR of 0.57. This indicates that female patients were more symptomatic compared with males, as documented in various studies(17–19). In the EORP AF Pilot Registry, palpitations and fear/anxiety were more common symptoms in female individuals, while no difference was found in other symptoms (e.g. dyspnoea, chest pain, fatigue, etc.) between both genders(18). Indeed, our results may indirectly reflect gender differences in the management of AF, regarding rate control or rhythm control. In EORP AF female AF patients with typical AF symptoms were more likely to receive rate control(18).

No statistical difference was found when we compared the age between asymptomatic and symptomatic AF patients. The prevalence of AF rises with increasing age(1) and given the

ageing general population, the number of AF patients is estimated to increase greatly(15). No previous study has reported the association between age and symptoms among AF patients.

Data coming from two major previous studies, both inserted in this present meta-analysis, had contrasting data on differences in mortality risk between asymptomatic and symptomatic patients. Boriani et al.(3) documented that asymptomatic AF patients had a significantly higher occurrence of death when compared with symptomatic patients. Conversely Flaker et al.(4) found that even after adjusting for previous major CV conditions, no difference in the risk of death was present between asymptomatic and symptomatic AF patients (hazard ratio 1.07, 95% CI 0.79-1.46, p = 0.67). Our data confirm that it's not possible to highlight any profound difference in overall mortality between patients with asymptomatic and symptomatic AF.

Even when focused on CV mortality, no difference was seen, despite AF patients having a high cardiovascular risk profile(20, 21). This risk is evident regardless of the symptom status, perhaps suggesting how AF patients need to be comprehensively treated, independently of symptomatic status.

The present meta-analysis underlines how the risk of thromboembolic events should not be based on the clinical status. Recent data on anticoagulant therapy in asymptomatic AF patients from the EORP AF Pilot Registry show that asymptomatic AF patients are similarly treated with anticoagulant therapy, compared to the symptomatic ones; however, if they had at least one symptomatic episode, fully asymptomatic patients were still significantly less treated with oral anticoagulants than those patients with one symptomatic episode(3). Indeed, fully asymptomatic AF patients were more likely treated with antiplatelet therapy regardless the higher thromboembolic risk(3).

Limitations

The principal limitation of the present meta-analysis is the reported high heterogeneity between the studies enrolled. This reflects the observational nature of four out of six studies selected. Even if this could affect the reliability of our results, the presence of observational studies still gives us insight into the "real-life" situation on the clinical burden of asymptomatic AF and its natural history.

In conclusion, asymptomatic AF is more associated with male sex, irrespective of age. Both general and cardiovascular death risks as well as thromboembolic risk do not seem to be affected by the asymptomatic clinical status. Symptomatic status should not determine our approach to stroke prevention and other cardiovascular prevention therapies, amongst patients with AF.

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FIGURE LEGENDS

Figure 1: Study selection process.

Figure 2: A comparison of symptomatic and symptomatic AF in female patients

(Event numbers refer to patient numbers).

Figure 3: Age differences comparing patients with asymptomatic AF and those with symptomatic AF.

Figure 4: All-cause death in patients with asymptomatic AF and those with symptomatic AF.

Figure 5: Cardiovascular death in patients with asymptomatic AF and those with symptomatic AF.

Figure 6: Comparison of TE events in patients with asymptomatic AF and those with symptomatic AF.

Figure 1

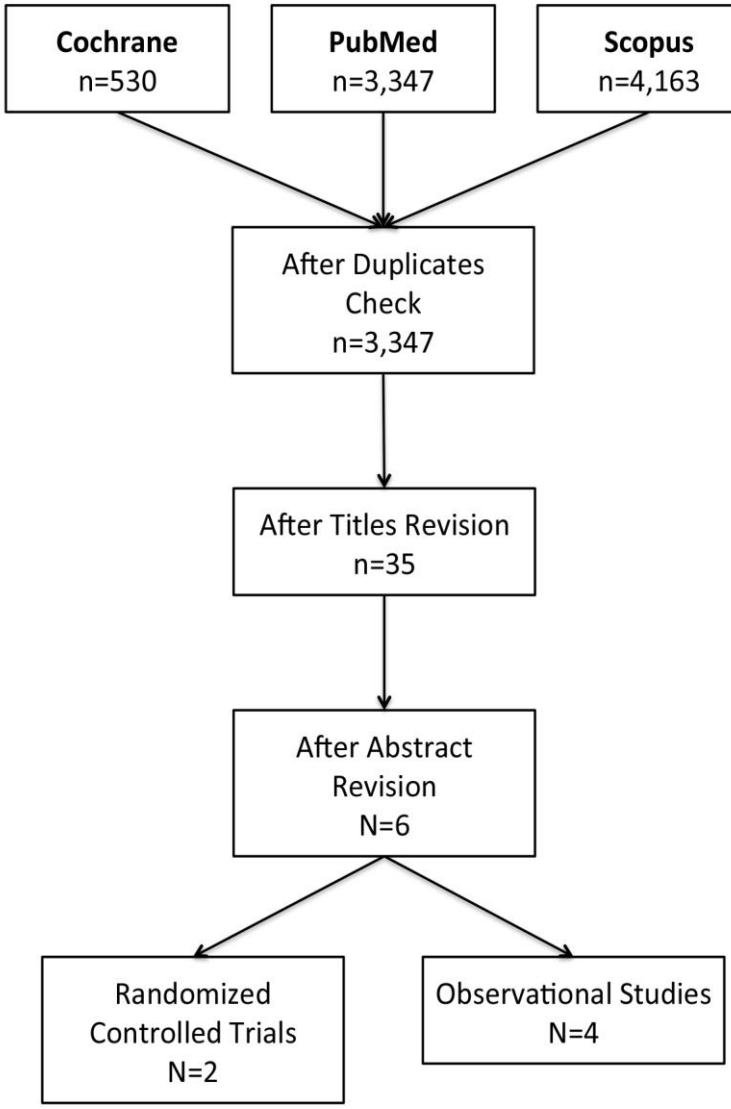

Figure 2

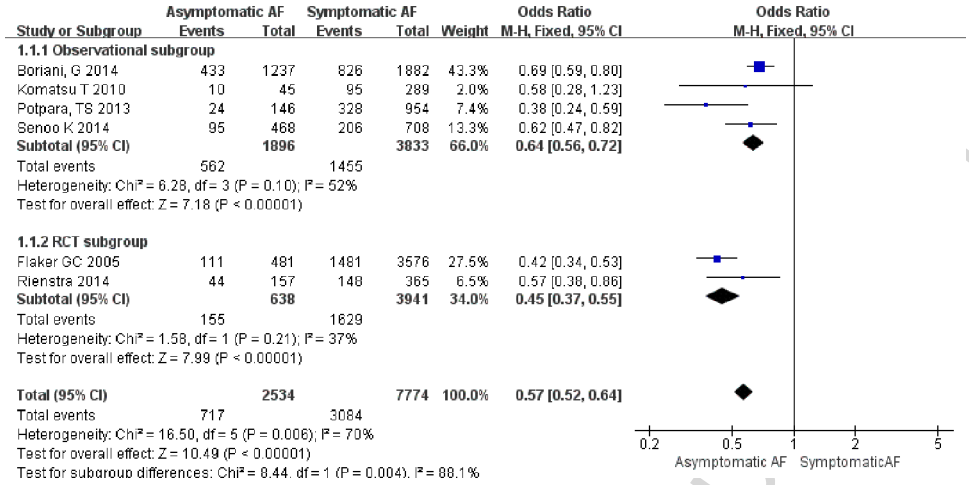

Figure 3

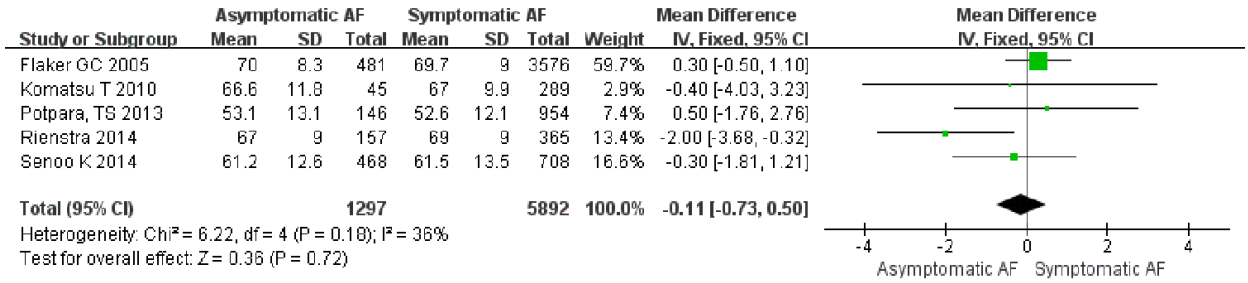

Figure 4

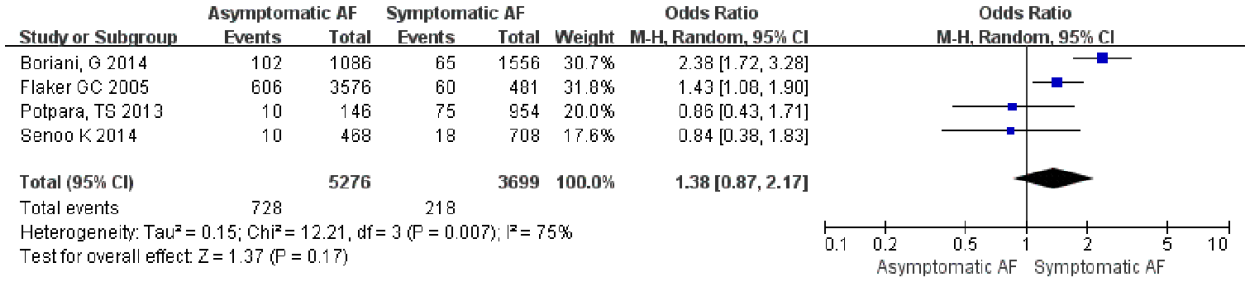

Figure 5

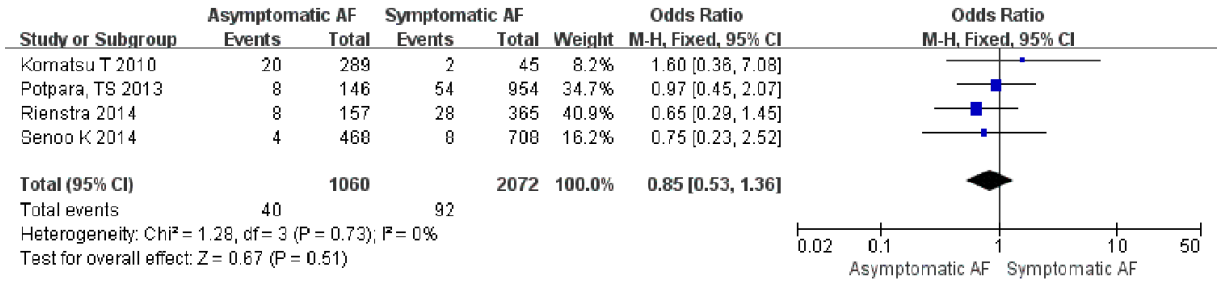

Figure 6

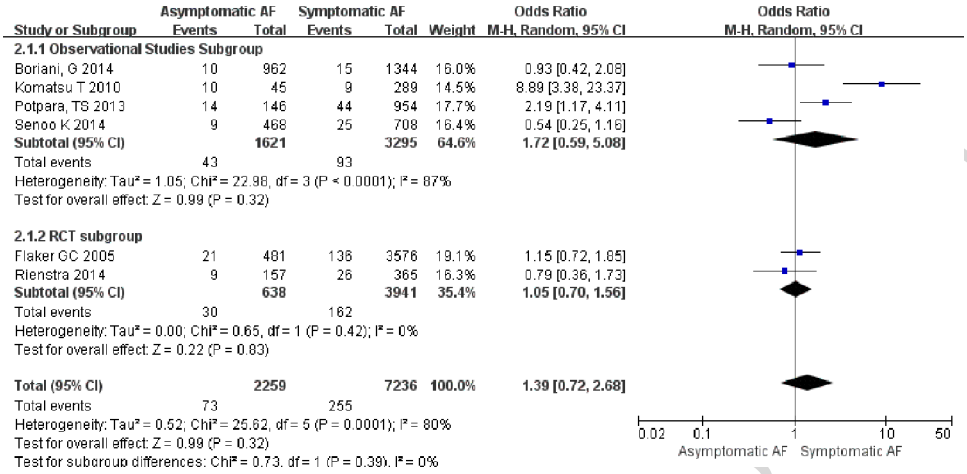

Table 1: Characteristics of the studies comparing asymptomatic and symptomatic AF patients.

STUDY	DATA SOURCE	ASYMPTOMATIC AF			SYMPTOMATIC AF			FU (Years)	OUTCOMES
		N	Age	Female (N)	N	Age	Female (N)		
Flaker, GC 2005 (4)	AFFIRM Trial	481	70±8.3	111	3,576	69.7±9	1481	3.5 (mean)	All death; Stroke
Komatsu, T 2010 (11)	Retrospective study	45	66.6±11.8	10	289	67.0±9.9	95	5.0±0.9	CV death; TE
Potpara, T 2013 (9)	Observational study	146	53.1±13.1	24	954	52.6±12.1	328	9.9±6.1	All death; CV death; TE; AF progression
Boriani, G 2014 (3)	EORP-AF Pilot Registry	1,237	72 (median)	433	1,882	68 (median)	826	1.0±0.1	All death; TE; CV hospitalization
Rienstra, M 2014 (8)	RACE Trial	157	67±9	44	365	69±9	148	2.3±0.6	QOL; CV death; TE
Senoo, K 2014 (10)	Shinken Database	468	61.2±12.6	95	708	61.5±13.5	206	3.3±2.5	Ischemic stroke; CV death; All death; AF progression

Legend: AF= Atrial Fibrillation; CV= Cardiovascular; TE= Thromboembolism; YRS= Years.

Table 2: Thromboembolic risk and antithrombotic treatment distribution in the studies comparing asymptomatic and symptomatic AF patients.

STUDY	ASYMPTOMATIC AF		SYMPTOMATIC AF	
	Thromboembolic Risk	Antithrombotic Treatment [Drug/Type (%)]	Thromboembolic Risk	Antithrombotic Treatment [Drug/Type (%)]
Flaker, GC 2005 (4)	NA	Aspirin (21) Warfarin (91)	NA	Aspirin (27) Warfarin (84)
Komatsu, T 2010 (11)	$CHADS_2$ 1.63 ± 1.27 (Mean)	Aspirin (42) Warfarin (24)	$CHADS_2$ 1.14 ± 1.18 (Mean)	Aspirin (28) Warfarin (24)
Potpara, T 2013 (9)	CHA_2DS_2-VASc ≥2 (32.9%)	Aspirin (47.9) VKAs (40.4)	CHA_2DS_2-VASc ≥2 (36.5%)	Aspirin (48.6) VKAs (21.3)
Boriani, G 2014 (3)	CHA_2DS_2-VASc ≥2 (84.7%)	Antiplatelets (32.3) Oral Anticoagulants (83.0)	CHA_2DS_2-VASc ≥2 (79.7%)	Antiplatelets (35.5) Oral Anticoagulants (81.2)
Rienstra, M 2014 (8)	$CHADS_2$ 1.2 ± 1.1 (Mean)	NA	$CHADS_2$ 1.7 ± 1.1 (Mean)	NA
Senoo, K 2014 (10)	CHA_2DS_2-VASc ≥2 (40.0%)	Antiplatelets (40.9) Oral Anticoagulants (33.8)	CHA_2DS_2-VASc ≥2 (47.0%)	Antiplatelets (39.2) Oral Anticoagulants (42.4)

Legend: AF= Atrial Fibrillation; CV= Cardiovascular; NA= Not Available; TE= Thromboembolism; VKAs= Vitamin K Antagonist; YRS= Years.

Table 3: Risk of bias evaluation

	Flaker, GC 2005 (4)	Komatsu, T 2010 (11)	Potpara, T 2013 (9)	Boriani, G 2014 (3)	Rienstra, M 2014 (8)	Senoo, K 2014 (10)
Selection Bias*	L	L	L	L	L	L
Performance Bias#	L	L	L	L	L	U
Attrition Bias¶	L	L	L	L	L	L
Detection Bias§	L	L	L	L	L	L
Reporting Bias^	L	L	L	L	L	L
Overall Risk of Bias	L	L	L	L	L	L

Legend: L= Low; U= Unclear.

* Randomization, allocation concealment, sequence generation, control for confounders in cohort studies;
# Fidelity to protocol, unintended interventions or co-interventions;
¶ Incomplete outcome data, intention-to-treat analysis, and completeness of follow-up;
§ Blinding of outcome assessors, especially with subjective outcome assessments, bias in inferential statistics, valid and reliable measures;
^ Selective outcome reporting evaluation by comparing study report and (a) protocol or (b) outcomes prespecified in methods.

HIGHLIGHTS

- Asymptomatic atrial fibrillation (AF) is more associated with male sex, irrespective of age.
- Asymptomatic clinical status doesn't seem to affect death risk as well as thromboembolic risk.
- Clinical status shouldn't determine our approach to pharmacological prevention strategies.